Author's response to reviews

Title: Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940-1998

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Author's response to reviews: see over
Dear Drs. Grandjean and Ozonoff:

Thank you for a speedy review process.

Our paper “Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940-1998,” revised in response to the comments of the peer reviewers, will be uploaded separately.

Reviewer #1, Dr. Pier Alberto Bertazzi, EPOCA, Epidemiology Research Center, University of Milan and Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena

Bertazzi Comment 1
The paper reports on the extension of the follow-up of a cohort of capacitor manufacturing workers employed in high exposure jobs in two plants in the USA. The topic is of interest since the toxic and carcinogenic effects of PCBs to humans are still incompletely known. The follow-up extension added a substantial number of person-years at risk and of deaths. State and county-specific reference rates were adopted to weight national rates. No quantitative exposure metrics and no individual job histories other than employment dates were available, and duration of employment in the two plants was used as a proxy for exposure to PCBs.

Results partially confirm findings of previous follow-up, but given the absence of individual quantitative exposure data they do not add much to our present knowledge.

It is a bit disappointing that the two potentially most interesting results (i.e., diseases of the nervous system and exposure-response relations) are not reported here, and are instead the object of other papers, one submitted elsewhere and one in preparation with a newly created job-exposure matrix.

Response
We did not use the job-exposure matrix to categorize exposure for this update for two reasons: (1) All the workers in this group were considered highly exposed, so the range of exposure levels/day would be much narrower than if all workers at the plant were in the analysis. (2) It was important to keep the analysis parallel to that done in the original analysis and the first update, which did not use a job-exposure matrix.

We agree with the reviewer’s other suggestion and have added results for the neurodegenerative diseases to the analysis (abstract, pp. 11, 14).

Bertazzi Comment 2
The consistently lower than expected results for breast cancer do probably deserve some further discussion in the light of previous data linking breast cancer and chlorinated compounds.

Response
We agree that the association between PCB exposure and breast cancer is still an open
question. Some time ago we initiated a study of breast cancer among women occupationally exposed to PCBs. An interview component was essential to obtain information on generally acknowledged breast cancer risk factors, such as parity and ages at menarche, first birth, and menopause. That manuscript is in draft form and we hope to submit it for publication within the year.

We have revised the discussion to add some of this information.

**Bertazzi Comment 5**
I’m not sure whether the reporting of both combined and plant specific results is needed: It very much depends on the design and the a priori hypothesis. Obviously, the choice should not be driven by results.

**Response**
We reported plant-specific and combined results to facilitate comparison between our results and those in the Brown 1987 update, which reported both plant-specific and combined results.

**Reviewer #2, Prof. Richard Clapp, Boston University School of Public Health**

**General**
This is a well-written study of an important cohort of PCB-exposed workers that substantially extends the follow-up.

**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)**
none

**Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)**
none

**Discretionary Revisions (which the author can choose to ignore)**

**Clapp Comment 1**
The reference on myeloma (#30) is a little out of date. There are new studies, including one by t'Mannetje, et al. (2005) that would be more relevant for readers of this paper. Likewise, the studies of breast cancer and PCB congeners by Demers, et al. (2002) and Zhang, et al. (2004) and of non-Hodgkin's lymphoma by DeRoos, et al. (2005) would bring the cited literature up to date.

**Response**
We have updated the discussion to include the more recent literature.

**Clapp Comment 2**
I don’t think 2-sided p-values are necessary in this article. There are published findings on this cohort and other PCB cohorts already in the literature reporting increased mortality from some of the same causes reported here (see Longnecker, et al. review in Annual Reviews of Public Health), so one-sided p-values would be appropriate. This is clearly discretionary, but even a Bayesian analysis with priors from the SMRs in the Longnecker, et al. meta-analysis might be preferable to 2-sided p-values.
Response
Since 95% confidence intervals were provided for each SMR, we removed all references to p-values in the tables, with the exception of the trend tests for duration of employment in Table 3.

Sincerely,
Avima Ruder